

## Epidemiology of food allergy

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Adverse reactions to foods can occur for a variety of reasons, but a food allergy is caused by a specific immune response. Challenges to determine the prevalence of food allergy include misclassification, biased participation, lack of simple diagnostic tests, rapid evolution of disease, large numbers of potential triggers, and varied clinical phenotypes. Nonetheless, it is clear that this is a common disorder, with studies suggesting a cumulative prevalence of 3% to 6%, representing a significant impact on quality of life and costs. The inclusion of mild reactions to fruits and vegetables could result in calculation of prevalence exceeding 10% in some regions. There are data from numerous studies to suggest an increase in prevalence, but methodologic concerns warrant caution. Prevalence varies by age, geographic location, and possibly race/ethnicity. Many childhood food allergies resolve. Population-based epidemiologic studies have generated numerous novel theories regarding risks, including modifiable factors such as components of the maternal and infant diet, obesity, and the timing of food introduction. Recent and ongoing studies provide insights on risk factors, prevalence, and natural course that may inform clinical trials to improve diagnosis, prevention, and treatment. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

**Key words:** Food allergy, prevalence, incidence, anaphylaxis, sensitization, peanut, milk, egg, shellfish, fish, nut, soy, wheat

The recent National Institute of Allergy and Infectious Diseases-sponsored expert panel report, "Guidelines for the Diagnosis and Management of Food Allergy in the United States,"<sup>1</sup> defines food allergy as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." In a publication summarizing the major findings of the literature review on which the guidelines are based,<sup>2</sup> it is stated that food allergy affects "more than 1-2% but less than 10%" of the population, and that it is "unclear" whether the prevalence is increasing. These conclusions clearly show that food allergy is a significant public health concern. However, the wide prevalence estimate of sufferers and the ambiguous statement about time trends present a somewhat disheartening conclusion

### Abbreviations used

DBPCOFC: Double-blind, placebo-controlled oral food challenge

OFC: Oral food challenge

SPT: Skin prick test

UK: United Kingdom

considering that there are hundreds of studies concerning the epidemiology of food allergy. Indeed, because of a myriad of factors, it is extremely challenging to determine food allergy prevalence with certainty. Here we explore some of the recent observations regarding the prevalence of food allergy as well as the nature of the limitations inherent in prevalence studies. Despite various methodologic limitations, the body of literature on topics of epidemiology of food allergy is extremely informative with regard to describing the scope of this problem as well as providing insights toward prevention, treatment, and diagnosis.

### LESSONS FROM EARLY STUDIES

Almost every scientific and lay article about food allergy begins with a comment about prevalence. For many years, the prevalence of adverse reactions to foods was summarized as affecting 6% to 8% of children on the basis of a study by S. Allan Bock, MD,<sup>3</sup> a study that has accumulated over 400 citations in the scientific literature. The prevalence of food allergy in the general population was often summarized as 1% to 2% on the basis of a study by Young et al,<sup>4</sup> which now has over 300 citations. These landmark studies were population-based and included supervised oral food challenges (OFCs), including double-blind, placebo-controlled oral food challenges (DBPCOFCs), considered a gold standard. It is informative to review these 2 studies because there are observations regarding methodologies that permeate almost all food allergy prevalence studies.

The study by Bock<sup>3</sup> recruited consecutive newborns from a private practice clinic in a "middle class" community in Colorado in 1980. A total of 480 children from an initial 501 completed the 3-year study (2 of 21 lost to follow-up had food-related complaints). Frequent questionnaires and contact with parents and physicians were used to identify adverse reactions attributed to foods, which were followed with unmasked OFCs, or DBPCOFCs if the results of unmasked challenges were uncertain. The natural course of reactions was monitored through repeated OFCs at intervals of 3 to 6 months among those who tested positive. There were 133 (28%) children with reported adverse reactions to foods other than fruit/juices (16% complained of fruit/juice reactions, and overall 12% of the cohort had symptoms verified on open challenge, ie, 75% of complaints were reproduced on open challenge). The symptoms during open challenges were not reported per patient, but among the 16 children with positive DBPCOFCs, symptoms were described with the following frequency: urticaria, 3;

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rash, 1; angioedema, 1; nasal congestion, 1; diarrhea, 10; vomiting, 6; and colic, 2. The extent of symptom combination and overlap is not stated, but one could note that a minimum of 11 participants did not have symptoms that would signify typical IgE-mediated reactions. The 16 children had 17 reactions confirmed in DBPCOFCs with the following frequency: milk, 11; peanut, 3; soy, 2; and egg, 1. Some children (43 total, not everyone challenged) were skin-tested, with only 4 positive skin prick tests (SPTs; 2 peanut, 1 egg, 1 milk), but all of these were among those with positive challenges. All but 4 allergies resolved by age 3 years.

This study included many aspects that are crucial to identifying food allergy prevalence: frequent assessments, consideration for any food ingested, and supervised food challenges. However, careful consideration of the study raises concerns that become pertinent to all studies of food allergy prevalence. It is highly likely that many of the reactions were not immune-mediated, at least not IgE-mediated, on the basis of symptoms and tests. It is often stated that patient-reported adverse reactions are not reproduced, but here 75% of fruit/juice reactions and 28% of other reactions were reproduced, and we do not know the length of time between initial symptoms and supervised feeding, which may exaggerate this discordance. For example, the study showed quick resolution of many of the challenge-confirmed reactions, and it is possible that delay in challenge from time of the complaint was a period of resolution. Foods that the child may not yet have ingested, or was instructed to avoid, may represent undiagnosed allergies.

The study by Young et al<sup>4</sup> was performed in the United Kingdom (UK) by using a questionnaire administered through random sampling to 15,000 households (approximately 40,000 persons). The date of the study was not noted, but the results were published in 1994. The study is notable as a population-based sample that included DBPCOFC, but final participation rates must be appreciated. Approximately 47% answered the survey, about 20% perceived adverse reactions, and, by design, half of the respondents were in the vicinity of the investigator and were asked for additional participation. About 40% invited to be interviewed agreed, and about half had symptoms relevant to specific foods/food groups that were targeted for food challenge (milk, egg, wheat, soy, citrus, fish/shellfish, peanut/nuts). Of 336 who might qualify for a food challenge, 47 were excluded for previous severe reactions, 128 declined, 161 were willing to participate, and 93 (32% eligible for challenge) underwent food challenges. On the basis of IgE tests and specific symptoms, 24 of the 47 not challenged because of severe symptoms were assumed reactive. Among those challenged, 18 people (19%) reacted with the following symptom frequencies: intestinal, 5; headache, 3; behavioral symptoms, 2; urticaria, 2; joint symptoms, 7; asthma, 1; and multiple symptoms, 4. Back-calculation to the entire population, making several assumptions about rates of reactions among persons not responding to the surveys, resulted in prevalence rates of 1.4% to 1.8%. About half of the self-reported reactions were to foods that were not included for consideration in food challenges. Interestingly, 45 "control" patients who described symptoms but did not perceive a problem were identified. Twenty-four were challenged, and 1 was positive. The authors point out that they likely have an underestimate because of foods not being tested, but also that they may underestimate or overestimate prevalence because of misclassification.

The strengths of this study include the large general population sample and application of screening tests followed by

DBPCOFC. As in the study by Bock,<sup>3</sup> it is implied that many persons avoiding foods would not react. However, it is evident that the majority of persons with complaints did not agree to, or did not complete, testing (perhaps in some instances from fear of reactions and a higher chance of having true reactivity). As in the study by Bock,<sup>3</sup> symptoms were often not ones typically associated with IgE-mediated reactions. In addition, nonparticipation in the survey might bias estimates of higher rates of allergy, whereas nonparticipation in testing might bias toward underestimates. This ambitious study demonstrates the many pitfalls of attempting to apply the gold standard diagnostic test of DBPCOFC to a population-based sample of the general population. Both of these studies accurately used terms of "adverse reactions" and "intolerance" and did not necessarily claim to have identified food allergy. The pitfalls demonstrated by these ambitious studies remain today as a caveat to performing accurate prevalence studies.

## RECENT META-ANALYSES AND LARGE SCALE REVIEWS

A systematic review by RAND Corp was performed by using prespecified criteria directed toward obtaining articles on epidemiologic aspects of food allergy<sup>5</sup> and resulted in the conclusion that food allergy affected from 1% to 2% up to 10% of the population.<sup>2</sup> Articles were identified from the United States and Canada (92); the UK, Australia, and New Zealand (58); Europe and Scandinavia (185); Mediterranean countries (31); Japan, Korea, and China (20); and others (34).

Prevalence of food allergy to cow's milk, hen's egg, peanut, fish, and shellfish was presented in a meta-analysis published in 2007 by Rona et al<sup>6</sup> as part of the EuroPrevall program. The EuroPrevall working group searched MEDLINE and EMBASE for articles from 1990 to 2005 and applied accepted criteria for quality and inclusion, resulting in 51 articles being included from 934 initially identified from a wide search strategy. The authors considered various degrees of evidence of food allergy including self-report, skin and serum tests, combinations of symptoms and test results, and OFC, and they also included age stratification. Considering studies of allergy to "any food" where multiple foods were assessed, the overall prevalence rates were 12% self-reported in children and 13% in adults (based on 23 studies), 3% for all ages on the basis of testing and history (6 studies), and 3% for all ages on the basis of studies that included DBPCFC (6 studies).<sup>6</sup> The studies had marked heterogeneity. For example, rates of self-reported allergy varied from 3% to 35%. In evaluating specific foods, the rates of self-report, symptoms with sensitization, and rates based on OFC were as follows, respectively: peanut (0.75%, 0.75%, not available), milk (3.5%, 0.6%, 0.9%), egg (1%, 0.9%, 0.3%), fish (0.6%, 0.2%, 0.3%), and shellfish (1.1%, 0.6%, not available). The report did not separate analyses for different age groups. However, for some of the foods, higher prevalence among children was evident; for example, 6% to 7% children self-reported milk allergy compared with 1% to 2% adults. The very wide ranges of prevalence estimates and lack of heterogeneity among studies, even after pooling of methods and stratification by age, underscores the potential that definitions, methods, and population characteristics impede the ability to compare studies.

In another report from the EuroPrevall working group, Zuidmeer et al<sup>7</sup> reviewed the prevalence of plant food allergies

including fruits, vegetables, legumes, tree nuts, wheat, cereals, soy, and seeds. They included 36 studies from 396 initially identified. Analyses were based on self-perception, test results, and OFC, but only 6 studies included OFC. Among the few studies including OFC, prevalence ranged from 0.1% to 4.3% each for fruits and tree nuts, 0.1% to 1.4% for vegetables, and <1% each for wheat, soy, and sesame. When evaluating reported symptoms or skin tests, which included far more studies, the ranges varied from nearly 0 to 4.2% for fruits, 2.7% for vegetables/legumes, 4.5% for tree nuts, 1.2% for wheat, and 0.6% for soy. The prevalence of perceived allergy generally exceeded prevalence of sensitization except for wheat and soy among adults. Similar to the previous EuroPrevall study, meta-analyses showed significant heterogeneity between studies regardless of food item or age group. A comprehensive review of milk allergy<sup>8</sup> summarized that milk allergy peaks in the first year of life and tends to subside.

## RECENT POPULATION-BASED STUDIES

A number of studies published since the time of the previously mentioned reviews<sup>6,7</sup> continue to provide insight on the scope of food allergies. Although they suffer from various limitations, these studies demonstrate the important public health aspects of food allergy.

### Rates of allergies to any foods

Venter et al<sup>9</sup> report on the rate of food allergies among a birth cohort of 969 children on the Isle of Wight, UK, evaluated at age 3 years. Testing included skin testing and OFCs that were offered when the food had not been eaten and positive tests were identified, or if an adverse reaction was reported (but not offered when SPT diameters were considered of a size diagnostic of allergy by the group's previous experiences). Foods included in a prescribed panel of tests at age 3 years and percent testing positive among 642 tested were as follows: milk (0.5%), egg (1.4%), wheat (1.3%), cod (0.5%), peanut (2%), and sesame (1.4%). Additional tests were performed on the basis of complaints in an attempt to include all possible allergies. The cumulative percentage of complaints of adverse food reactions was 33.7% at 3 years, with 8% having a current complaint, with systems involved being cutaneous, followed by gastrointestinal, and more rarely respiratory. Using unmasked OFCs and a clear history, the cumulative incidence was 6%, and using DBPCOFCs, 5%; the primary triggers were milk, egg, and peanut. Although the authors explain that their results are comparable to those of the study by Bock<sup>3</sup> performed about 20 years earlier, subtle differences in the UK study compared with the earlier US study included: more reactions described to include skin rather than gastrointestinal symptoms; lower rates of consent for OFC or DBPCFC (46% and 86% respectively at age 3 years, including refusal by children with positive tests and history of symptoms on exposures); and no performance of OFC on children with large positive skin tests (9 children). Thus, it may be argued that the study by Venter et al<sup>9</sup> found a greater proportion of children with likely IgE-mediated allergies compared with the study by Bock.<sup>3</sup>

Osterballe et al<sup>10</sup> evaluated 1272 young adults age 22 years in Odense, Denmark, by using questionnaires, SPTs, and OFCs. By questionnaire, 20% reported adverse reactions to non-pollen-associated foods, which after OFC (performed in 42 cases among 165 with complaints) resulted in a prevalence of 1.7%. The low

rate of challenges may have led to underestimates. Regarding pollen-associated foods, 17% reported symptoms (83% had oral symptoms), representing 74% of those describing possible pollen allergy. In a study of a birth cohort of 562 children also from Odense<sup>11</sup> evaluated periodically with interviews, SPT, food-specific IgE, and OFC (offered for suspicion of allergy or positive tests without ingestion) to age 6 years, overall, 3.7% had positive food challenges to 1 or more foods.

Several studies have used indirect means to estimate food allergy prevalence in the United States. Liu et al<sup>12</sup> took advantage of the serologic testing performed during the National Health and Nutrition Examination Survey in the United States from 2005 to 2006. Estimations of clinical food allergy risk were based on previous studies correlating clinical outcomes to food-specific IgE concentrations. The rates of clinical food allergy varied by food type and age group and overall showed the following: milk, 0.4%; egg, 0.2%; peanut, 1.3%; and shrimp, 1%. In the children age 1 to 5 years, clinical allergies to milk, egg, and peanut were estimated at 1.8% each. On the basis of these 4 foods only, overall food allergy prevalence was estimated at 2.5%. Branum and Lukacs<sup>13</sup> reported that in 2007, on the basis of the National Health Interview Survey response to the query, "During the past 12 months has [child] had any kind of food or digestive allergy?" 3.9% of US children were affected. Analyses of data from 2441 mothers in the 2005 to 2007 US Infant Feeding Practices Study II,<sup>14</sup> which followed newborns to age 1 year and defined probable food allergy as doctor-diagnosed or immediate food-related symptoms (likely urticaria/angioedema), found a rate of 6% (milk, 3.8%; soy, 1.4%; fruit, 1.2%; peanut, 0.6%; wheat, 0.5%).

### Prevalence of specific allergies

A number of large population-based studies have recently addressed a topic of pressing interest, the prevalence of peanut allergy.<sup>15</sup> Three studies used a random calling methodology with administration of a survey, with methodologic variations among the studies. In a Canadian study,<sup>16</sup> self-reported peanut allergy in children was 1.77%, and in adults, 0.78%; these values decreased as stricter criteria were applied (1.68% and 0.71% for "probable" and 1.03% and 0.26% for "confirmed allergy," although this latter definition required supporting documentation that was not accessible for the majority of participants). The US study<sup>17</sup> result was 1.4% for children and 0.6% for adults. With similar methods used in Singapore, but directed to children 4 to 6 years old, 3.6% of natives and 3.2% of expatriates reported peanut allergy, but when a convincing history was used, the percentages were 0.64% and 1.29%, respectively.<sup>18</sup> Although the rates of estimated peanut allergy in these various studies appear spectacularly high, a UK birth cohort study that included testing and OFCs also arrived at a rate nearing 2%.<sup>19</sup> Ben-Shoshan et al<sup>20</sup> evaluated peanut allergy among kindergarten to grade 3 schoolchildren in Montreal, Quebec, Canada. The study applied allergy tests, including DBPCOFC when possible. Among 5161 families responding to the survey (64.2% response rate), after adjustment for missing data, an estimated 1.62% of the cohort (95% CI, 1.31% to 1.98%) had peanut allergy. In a retrospective study of peanut allergy based on specialist referral and evaluations in the Australian Capital Territory, the estimated minimum incidence of peanut allergy in children by age 6 years born in 2004 was 1.15%.<sup>21</sup> A validated questionnaire was used to determine peanut allergy rates in a school age cohort of Israeli Jewish children

( $n = 5615$ ), finding a rate 0.17%; the result was 10-fold lower than that in a cohort of Jewish children in the UK ( $n = 5171$ , 1.85%;  $P < .001$ ).<sup>22</sup> It is remarkable that the studies are consistent among several direct and indirect methodologies used in Canada, the United States, Australia, and the UK, agreeing that peanut allergy affects more than 1% of children. The reasons for lower rates among those native to Singapore and Israeli Jews remain speculative,<sup>15</sup> but it is interesting that a milk allergy study in Israel<sup>23</sup> concluded that 0.5% of 13,019 infants had IgE-mediated milk allergy, raising the point that allergy rates in general may be lower in Israel.

Several of the recent telephone survey studies reviewed here<sup>16-18</sup> and another study<sup>24</sup> also evaluated allergy rates for tree nut (Canada, 1.1%, probable; United States, 0.6%, self-report; Singapore, age 14-16 years, 0.8%, self-report), sesame (0.1% self-reported in the United States and Canada), fish (Canada, 0.48%, probable; United States, 0.4%, probable), and shellfish (Canada, 1.42%, probable; United States, 2%, probable; Singapore, age 14-16 years, 5.2%, convincing history). It is interesting to note that many of the rates are similar. In the Singapore study, it was noted that rates of confirmed shellfish allergy were significantly higher and tree nut allergy rates significantly lower in the children native to Singapore compared with expatriates. These studies and others<sup>25</sup> reveal that specific allergy rates likely vary by local diet, environmental factors, and possibly genetics.

### THE SELF-REPORT, SELF-PERCEIVED CONUNDRUM

As pointed out in the recent large reviews, guidelines, and meta-analyses,<sup>6,7,26</sup> “self-perceived” adverse reaction rates exceed rates based on OFCs. The discordance has been described in various ways. For example, the new US guidelines summarize a self-report rate of 12% to 13% compared with about 3% when testing and or DBPCOFC is performed.<sup>1</sup> Individual studies show stronger discrepancies when considering OFC results. For example, the landmark pediatric study by Bock<sup>3</sup> indicates 28% reporting symptoms (parent or doctor reports), but only 28% of those with complaints were verified on OFC. In the study by Young et al,<sup>4</sup> 19% of the complaints were verified on challenges.

These discrepancies should lead physicians to evaluate patient complaints with attention toward expanding the diet, knowing that many complaints will not be verified. However, the media sometimes misconstrues the discrepancy to claim that reports of food allergy are exaggerated. It can be argued that this is an inaccurate representation because most of the studies are focusing on adverse reactions to foods, not allergies. It is not surprising that the lay public might use the term “allergy” to describe any adverse response to foods. Technically, it is not always possible to confirm an immune etiology. In addition, as reviewed here, the discrepancy may be exaggerated more by persons with likely allergy not participating in (agreeing to) OFCs. Another source of the discrepancy is the possibility that the adverse reaction was related to the food, perhaps even a true allergy, but resolved before additional testing. This possibility is underscored by studies in which serial surveys and food challenges were performed and showed that the child had resolution of allergy in a short time frame, such as 6 months.<sup>3,27</sup> Interestingly, for foods that typically are responsible for persistent and severe allergies (eg, peanut, nuts, seafood), the rates of self-perceived allergy are close to the rates of allergy when stricter criteria are applied.<sup>16,24</sup> There

**TABLE I.** Examples of challenges in performing population-based food allergy prevalence studies

Challenge	Examples of considerations/pitfalls
Participation	May bias to include those more likely affected Requires consideration of differential participation Differential dropout on the basis of procedures
Timing/frequency of evaluations	Allergy may resolve or develop Incidence vs prevalence
Food targeted	Different natural history, severity, exposures
Method of diagnosis	History, testing, types of tests, interpretation of tests (including interpretation of OFC)
Data analyses	Management of missing data, sensitivity analyses
Definition of allergy	IgE-associated vs any immune response vs clinical outcome of OFC
Exposure to triggers	Accounting for differential exposure in the population
Severity	Whether to include range of responses
Size of study	Costs, accuracy

are also individuals identified who had not been reporting an allergy because they were not previously exposed to a food but reacted when exposed during a study.<sup>4,28</sup> In summary, the discrepancy between reported adverse food reactions and verified reactions should keep physicians alert to the possibility that additional testing and challenge might result in diet expansion; however, care must be exercised in discussing public perceptions of “allergy.”

### CHALLENGES IN DETERMINING PREVALENCE OF FOOD ALLERGY

With review of various studies, we have noted a variety of limitations in determining prevalence or incidence. Indeed, there are numerous nuances that hinder accurate assessments. The limitations include definitions of food allergy and a variety of methodologic concerns. Some of the challenges are summarized in Table I.

#### Definitions of allergy

It is important to attempt to define a phenotype of disease when determining prevalence. If food allergy is defined as per the new US guidelines<sup>1</sup> as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food,” there are a number of ramifications to prevalence studies. Some clear allergic responses (eg, anaphylaxis supported by positive test) will not be purposefully reproduced for practical and ethical reasons. Proving an immune mechanism for each individual participant may pose a challenge, considering the varied phenotypes and pathophysiology of food allergy. It is important to describe the phenotypes included in prevalence studies. Oral allergy syndrome/pollen food-related allergy clearly fulfills this definition of an allergy but is often not focused on when statistics are offered regarding food allergy. In a study of young adults in Odense, Denmark, 16.7% reported this type of allergy.<sup>10</sup> If 10% to 25% of the population has pollen-associated rhinitis<sup>29</sup> and 47% to 70% of persons with pollen allergy experience pollen-related food allergies,<sup>30</sup> then 5% to 19% in some regions may



be affected by this common food allergy that is often neglected when discussing prevalence.

## Methodologies

As partly reviewed in Table I, there are limitations to any method used to ascertain cases of food allergy in the general population. When testing is used, even to address IgE-mediated food allergy, there are clearly limitations regarding the fact that tests might be positive when a food is tolerated or negative when it is not tolerated. Interestingly, in evaluation of sensitization to foods in the European Community Respiratory Health Survey, in which 4522 young adults from 13 countries were tested with up to 24 foods,<sup>31</sup> sensitization rates ranged from 24.6% in Portland, Ore, to 7.7% in Reykjavik, Iceland, and correlated with total IgE. Sensitization patterns otherwise appeared similar, with the most common foods being hazel, peach, shrimp, wheat, apple, sesame, carrot, kiwi, celery, corn, tomato, rice, and buckwheat (from 7.2% to 2.8%), peanut (2.6%), and banana, walnut, sunflower, soy, poppy, melon, mustard, milk, egg, and fish (from 2.5% to 0.2%). It is interesting that pollen and perhaps dust mite-related foods are the ones most commonly identified regarding sensitization, raising the possibility that these tests reflect allergies to environmental proteins. Although patterns were similar, the rate of sensitization to peanut in the United States was 9.3%, and in the UK, 1.5%. Clearly, many sensitized persons have no symptoms. As noted previously, on the basis of limited studies that have correlated allergy outcomes to food-specific IgE levels, estimations of allergy could be made but clearly do not represent confirmed allergy that would require more data about history or tests.<sup>12</sup>

Using DBPCOFC to confirm reactions presents huge obstacles for prevalence studies. The format is time-consuming, not all foods are easily masked, and using this single outcome as a marker of food allergy would greatly underestimate allergy. Barriers to using DBPCOFC in population-based studies are not unexpected considering the technique is not used for clinical care in many children who are reasonably diagnosed on the basis of factors such as history, test results, and unmasked OFCs.<sup>32</sup> However, ambitious studies are underway using nested case-control designs and multinational birth cohorts under the EuroPrevall program that follow up symptomatic individuals (and selected controls) for testing and DBPCOFC by using extremely comprehensive schemes.<sup>33,34</sup> It may be possible to increase certainty of diagnosis by using additional factors and schema.<sup>35,36</sup>

## IS FOOD ALLERGY INCREASING IN PREVALENCE?

Consider an amusing example. In 1998, there were 20 abstracts presented at the American Academy of Allergy, Asthma & Immunology annual meeting referenced under the key word "food allergy." In 2009, there were 201 such abstracts, a 10-fold increase. This increase may represent better indexing, a response to increasing prevalence, an increase in researchers or funding, other factors, or a combinations of reasons. It is not likely that the increase simply reflects a 10-fold increase in food allergy prevalence. This simple example reflects the difficulty in trying to assess changes in prevalence. At a minimum, methodologies should be the same and populations should be similar when trying to evaluate time series. Power is also a problem, because the rates of specific allergies are often low. Anecdotal examples implying an increase in prevalence are interesting to entertain. It can be argued that 30 years ago, if children had peanut allergy, it is

unlikely they would not have been diagnosed because eating the food would have caused obvious symptoms. Now, for example, parents frequently remark that they never recalled food allergy among their classmates, but there are numerous children in their own children's schools with food allergies. A telephone survey of 400 school nurses revealed that 44% reported an increase in food allergies in their schools over the preceding 5 years.<sup>37</sup> Although the anecdotes are compelling, solid evidence remains elusive.

There are several studies in which similar methods are applied over time, mostly focusing on peanut. We performed a random calling telephone survey regarding peanut and tree nut allergy across the United States using the same methodologies in 1997, 2002, and 2008.<sup>17</sup> The rates of surrogate-reported allergy in children increased significantly for tree nuts (0.6%, 1.2%, and finally 2.1%) and for peanut (0.4%, 0.8%, and finally 1.4%). Limitations of the studies included self-report, decreasing participation rates, and self-assessment of allergy with an inability to control for increasing awareness as an explanation. In a retrospective study of peanut allergy based on specialist referral and evaluations in the Australian Capital Territory, the estimated minimum incidence of peanut allergy in children by age 6 years born in 2004 was 1.15%, compared with an estimate of 0.73% for those born in 2001.<sup>21</sup> Peanut sensitization and allergy rates were reported from 3 birth cohorts from the Isle of Wight, UK. Grundy et al<sup>38</sup> reported peanut sensitization and reactivity in a birth cohort of children 3 and 4 years old on the Isle of Wight born from 1994 to 1996, and compared the results with those of a cohort born in 1989, evaluated at age 4 years. They documented a nonsignificant 2-fold increase in reported peanut allergy (0.5% to 1.0%;  $P = .17$ ) and a 3-fold increase in sensitization (1.1% to 3.3%;  $P < .001$ ). After analysis that included oral challenges, the total estimate for clinical peanut allergy was 1.5% among the 1994 to 1996 cohort. Venter et al<sup>39</sup> compared these results to a third cohort born between 2001 and 2002 evaluated at 3 years of age and found sensitization rates of 2% and reaction rates of 1.2%, indicating a leveling off or slight but insignificant decline. The 3 cohorts are not entirely similar because ages and participation rates varied. Ben-Shoshan et al<sup>20</sup> followed up a 2000 to 2002 cross-sectional prevalence study, evaluating peanut allergy from 2005 to 2007 among kindergarten to grade 3 schoolchildren in Montreal, Quebec, Canada. Among 5161 families responding to the survey (64.2% response rate), after adjustment for missing data, an estimated 1.62% of the cohort (95% CI, 1.31% to 1.98%) had peanut allergy compared with 1.34% (95% CI, 1.08% to 1.64%) 5 years earlier ( $P =$  nonsignificant). In a national database of the English population queried for clinician-recorded diagnosis of peanut allergy,<sup>40</sup> from 2001 to 2005 there was an increased prevalence of peanut allergy but not increased incidence; overall, the database showed prevalence rates in the range of 0.2% to 1%. In summary, there are mixed results regarding an increase, but it is notable that multiple studies show rates over 1% in children.

A few studies have focused on time series of any forms of food allergy. In a study from the same clinic in China performed in 1999 and 2009, rates increased from 3.5% to 7.7% ( $P = .017$ ).<sup>41</sup> Branum and Lukacs<sup>13</sup> reported on several US national databases in which information could be compared over time. Based on the response to, "During the past 12 months has [child] had any kind of food or digestive allergy?" there was an 18% increase from 1997 to 2007. On the basis of diagnostic coding in US national ambulatory care surveys, ambulatory care visits tripled between 1993 and 2006 ( $P < .01$ ). However, it remains uncertain whether

increases represent differences in awareness and coding or true increased prevalence. Reports of increased emergency department visits over time suffer from similar limitations.<sup>42</sup> An increasing failure of children to resolve food allergies promptly, on the basis of the potentially biased observations of a referral practice,<sup>43-45</sup> could contribute to an increasing prevalence. In summary, there is compelling evidence for an increase in food allergy prevalence, as has been noted for other atopic conditions, but confirmatory studies are lacking.

## ANAPHYLAXIS AND FATALITIES

Determination of the prevalence of food-related anaphylaxis is hindered by definitions of diagnosis, acquisition of cases through various methodologies, and many of the limitations that affect prevalence as previously reviewed. Food generally appears to be the most common trigger of anaphylaxis in the community, and arguments have been made that anaphylaxis has increased.<sup>46</sup> In the United States, comparison of results of similar methodologies in a similar geographic region in Minnesota from 1983 to 1987 and 1993 to 1997 potentially show a 71% to 100% increase.<sup>46-48</sup> The proportion of anaphylaxis attributed to foods (about one third) was generally similar over time between and within these studies. Studies focusing on pediatric food-related ambulatory and emergency department visits or food-induced anaphylaxis suggest increases as well.<sup>42,49,50</sup> Data from 34 emergency departments in the US National Electronic Injury Surveillance System were analyzed for food-related adverse events over August and September 2003.<sup>50</sup> Extrapolating from the available data, there were 20,281 emergency department visits, 2333 episodes of anaphylaxis, and 520 hospitalizations for food allergy reactions in the United States over this 2-month period. For adults, shellfish was the most common trigger, whereas egg, fruits, peanuts, and tree nuts were more common triggers for young children. In a review by de Silva et al<sup>51</sup> of 117 pediatric patients presenting with anaphylaxis to 1 hospital in Melbourne, Australia, food was responsible for 85% of reactions, and peanut (18%), cashew (13%), and milk (11%) were the most common triggers. Clark et al<sup>52</sup> reviewed data from 2 US emergency department–based cohort studies and the US National Hospital Ambulatory Medical Care Survey and estimated 203,000 emergency department visits per year (for 2001–2005; 38% pediatric), classifying approximately 90,000 as probable anaphylaxis.

There are no studies to address directly the prevalence of fatal food-allergic reactions. Lacking any direct studies, and extrapolating from the US population-based study of anaphylaxis by Yocum et al,<sup>47,53</sup> in which there was 1 death related to exercise and about 36% of anaphylaxis was food-related, an estimate of 150 deaths per year in the United States had been proposed.<sup>54</sup> The follow-up study by Decker<sup>48</sup> in the same region did not disclose any deaths. The review by de Silva et al<sup>51</sup> noted 1 death among the 117 children with anaphylaxis (caused by peanut in a 7-year-old). In a US registry that was not comprehensive or population-based, 31 deaths were registered from 2001 to 2006.<sup>55</sup> In a more comprehensive fashion, Pumphrey and Gowland<sup>56</sup> sought to ascertain all food-related anaphylactic deaths in the UK from 1999 to 2006 and found 48. These 2 studies primarily revealed important risk features including age (adolescents and young adults), delayed use of epinephrine, and comorbid asthma. Among the 79 deaths, 11 were children age 10 years and under. Simon and Mulla<sup>57</sup> used death certificate diagnostic

**TABLE II.** Observations about food allergy (or in some cases other atopic diseases) gleaned from general population-based epidemiologic studies

Risk factor	Observation (examples)
Genetics	Increased risks for siblings, HLA, specific genes
Sex	Increased risk for boys, possibly women
Associated atopic disease	Atopic dermatitis, comorbid food allergies Asthma for increased severity of reactions
Exposure route	Theory that lack of ingestion exposure during period of environmental exposure may increase risk
Maternal ingestion	Controversy about maternal ingestion of allergen during pregnancy/lactation being risk factor
Infant ingestion of allergen	Recent studies supporting earlier ingestion of allergen as protective Frequency, dose may be a factor
Dietary constituents	Fatty acid profile may be risk/protective
Vitamin D	May be protective
Obesity	May be risk factor (inflammatory state)
Hygiene hypothesis	Increased risk for cesarian section, antibiotics Reduced risk more siblings, child care, pets, rural/farm
Race/ethnicity	Nonwhite may be risk
Geography/diet	Pollen exposure may drive differences Dietary differences (eg, roasted peanut compared with boiled)

codes in Florida over a period from 1996 to 2005 and calculated an annual anaphylaxis fatality rate of 5 in 10 million. A trigger was noted for 52% of the deaths, and among those, 16% were related to food (peanut in 4 persons age 25–64 years; 1 adult each for shellfish, mango, and food additive). Extrapolation from this study, assuming an equivalent proportion of food triggers in the unknown group, would estimate roughly 1 in 12 million deaths from food allergy. Liew et al<sup>58</sup> reviewed national databases to evaluate anaphylaxis fatalities and hospital admissions in Australia from 1997 to 2005. Although food-induced anaphylaxis admissions increased 350% over this period, food anaphylaxis fatalities did not appear to increase. Fatality rates were approximately 0.64 per million inhabitants per year, and by extrapolation, 6% of them were food-related. Seven food-induced fatalities were noted, and all victims were between age of 8 and 35 years, although food anaphylaxis hospital admissions were primarily among children under age 5 years. Considering that food-related fatalities are rare and potentially underdiagnosed (eg, could be attributed to asthma or different triggers), it is difficult to estimate an incidence rate.

## EPIDEMIOLOGY: BEYOND PREVALENCE

*Epidemiology* refers to the study of patterns of health and associated factors at the population level. A variety of population-based studies have generated new hypotheses about risk factors for food allergy.

### Risk factors, genetics, and racial and ethnic differences

Epidemiologic studies have recently provided data on a number of emerging thoughts about risks and causes of food

**TABLE III.** Summary of estimated prevalence rates based upon recent studies reviewed

Target food	Prevalence
Major allergens or comprehensive	<i>Comprehensive literature review: "more than 1-2% but less than 10%"<sup>2</sup></i> <i>Self-report, 12% to 13%<sup>1,6</sup></i> <i>Overall population, 3%*<sup>1,6</sup></i> <i>General population (4 foods), 2.5% (US)<sup>12</sup></i> <i>Age 1 y, 6% (US)<sup>14</sup></i> <i>By age 3 y, 5% to 6%* (UK)<sup>9</sup></i> <i>Through age 6 y, 3.7%* (Denmark)<sup>11</sup></i> <i>Children, 3.9% (US)<sup>13</sup></i> <i>Age 22 y, 1.7%* (Denmark)<sup>10</sup></i>
Milk	<i>Overall, 0.9%*<sup>6</sup></i> <i>General, 0.4% (US)<sup>12</sup></i> <i>Age 1 y, 3.8% (US)<sup>14</sup></i> <i>By age 3 y, 2.9%* (UK)<sup>9</sup></i> <i>Age 1-5 y, 1.8% (US)<sup>12</sup></i> <i>By age 3-5 y, 0.5%* (Israel)<sup>23</sup></i>
Egg	<i>Overall, 0.3%*<sup>6</sup></i> <i>Overall, 0.2% (US)<sup>12</sup></i> <i>Age 3 y, 2%* (UK)<sup>9</sup></i> <i>Age 1-5 y, 1.8% (US)<sup>12</sup></i>
Peanut	<i>Overall, 0.75%<sup>6</sup></i> <i>Overall, 1.3% (US)<sup>12</sup></i> <i>Children, 1.7% (Canada)<sup>16</sup>; 1.4% (US)<sup>17</sup>; 1.9% (UK)<sup>22</sup>; 0.2% (Israel)<sup>22</sup></i> <i>Adults, 0.7% (Canada)<sup>16</sup>; 0.6% (US)<sup>17</sup></i> <i>Age 1 y, 0.6% (US)<sup>14</sup></i> <i>By age 3 y, 1.2%* (UK)<sup>9</sup></i> <i>Age 4-6 y, 0.6% (Singapore)<sup>18</sup></i> <i>Age 1-5 y, 1.8% (US)<sup>12</sup></i> <i>Age 5-8 y, 1.6%* (Canada)<sup>20</sup></i> <i>By age 6 y, 1.2% (Australia)<sup>21</sup></i>
Tree nuts	<i>Overall, 0.1-4.3%*<sup>7</sup>; up to 4.5% (SPT); up to 8.5% (symptoms)<sup>7</sup></i> <i>Overall, 1.1% (Canada)<sup>16</sup>; 0.6% (US)<sup>17</sup></i> <i>Adults, 0.5% (US)<sup>17</sup>; 1% (Canada)<sup>16</sup></i> <i>Children, 1.1% (US)<sup>17</sup>; 1.6% (Canada)<sup>16</sup></i> <i>Age 14-16 y, 0.8% (Singapore)<sup>18</sup></i>
Fish	<i>Overall, 0.3%*<sup>6</sup></i> <i>Overall, 0.5% (Canada)<sup>16</sup>; 0.4% (US)<sup>17</sup></i> <i>Age 3 y, 0.5%* (UK)<sup>9</sup></i> <i>Adults, 0.6% (Canada)<sup>16</sup>; 0.5% (US)<sup>17</sup></i> <i>Children, 0.2% (Canada, US)<sup>16,17</sup></i>
Shellfish	<i>Overall, 0.6%<sup>6</sup></i> <i>Overall, 1% (US)<sup>12</sup>; 1.4% (Canada)<sup>16</sup>; 2% (US)<sup>17</sup></i> <i>Adults, 1.7% (Canada)<sup>16</sup>; 2.5% (US)<sup>17</sup></i> <i>Children, 0.5% (Canada, US)<sup>16,17</sup></i> <i>Age 14-16 y, 5.2% (Singapore)<sup>18</sup></i>
Soy	<i>Overall, 0 to 0.7%*<sup>7</sup></i> <i>Age 1 y, 1.4% (US)<sup>14</sup></i>
Seeds	<i>Overall, &lt;1%*<sup>7</sup></i> <i>Overall, 0.1% (US, Canada)<sup>16,17</sup></i> <i>By age 3 y, 0.6%* (UK)<sup>9</sup></i>
Wheat	<i>Overall, 0 to 0.5%*, up to 1.2% (SPT); up to 1.3% (symptoms)<sup>7</sup></i> <i>Age 1 y, 0.5% (US)<sup>14</sup></i> <i>By age 3 y, 0.4%* (UK)<sup>9</sup></i>
Fruits	<i>Overall, 0.1 to 4.3%*; up to 4.2% (SPT); up to 8.5% (symptoms)<sup>7</sup></i> <i>Age 1 y, 1.2% (US)<sup>14</sup></i>

(Continued)

**TABLE III.** (Continued)

Target food	Prevalence
Vegetables	<i>Overall, 0.1 to 0.3%*, up to 2.7% (SPT); up to 13.7% (symptoms)<sup>7</sup></i>
Oral allergy (raw fruits/vegetables)	<i>Age 22 y, 17% (Denmark)<sup>10</sup></i>

*Overall* refers to any ages, point prevalence. *Italics* indicate meta-analysis or review of multiple studies.

\*OFC performed on at least a subset. See text for details.

allergy. Lack<sup>59</sup> recently reviewed epidemiologic risk factors for food allergy, which include genetic risks (familial associations, HLA, and specific genes), association with atopy (eg, atopic dermatitis), timing of exposure to allergen, route of exposure (eg, topical/respiratory exposure may be sensitizing), reduced consumption of  $\omega$ -3 polyunsaturated fatty acids, and the hygiene hypothesis. Another risk may be antacid medications that alter digestion and may allow increased immune exposure to ingested proteins.<sup>60</sup> Vassallo and Camargo<sup>61</sup> reviewed the mechanisms for the hypothesized link between vitamin D and food allergy. Recent epidemiologic study findings, such as the observations that season of birth is a risk factor,<sup>62</sup> that food-induced pediatric anaphylaxis is more common in northern areas of the United States,<sup>63</sup> and that maternal intake of vitamin D during pregnancy was associated with a decreased risk of food sensitization,<sup>64</sup> continue to support the hypothesis.

Racial and ethnic differences have not been explored widely. In telephone surveys, shellfish allergy was reported at a significantly higher rate among black/African American subjects than white subjects (3.1% vs 1.8%).<sup>24</sup> Non-Hispanic blacks also had increased risks of having serologic results indicating likely food allergy in the National Health and Nutrition Examination Survey study (odds ratio, 3.1).<sup>12</sup> Several studies have indicated that having food allergy may be a risk for problematic asthma, and having asthma may be a risk for severe/fatal food allergy.<sup>12,54,65</sup> Boys appear to be at higher risk than girls,<sup>12</sup> and perhaps women more than men.<sup>66</sup> One study showed a higher risk for increased affluence.<sup>40</sup> Obesity may be an inflammatory state associated with increased risk for food allergy as well.<sup>67</sup> An increasing number of epidemiologic studies support the notion that delaying exposure to allergenic foods in infancy and early childhood may be a risk factor for food allergy.<sup>22,23,68</sup> However, the full implications of exposures *in utero*, during lactation, and after birth remain areas with controversy and active investigation.<sup>69,70</sup> A summary of selected observations is shown in Table II. Controlled trials are needed to explore cause-and-effect relationships.

## FUTURE DIRECTIONS

Although there remains uncertainty about the exact prevalence and incidence of food allergies, it is clear that the disease is common and impactful and likely has increased in prevalence similar to other atopic diseases. A summary of prevalence based on studies highlighted in this review is shown in Table III. Large-scale studies have also disclosed that the rate of allergy varies geographically, likely primarily on the basis of various environmental/dietary factors. Knowledge about the most common triggers is helpful in approaching diagnosis because attention may be focused on the most likely causes. Epidemiologic studies have disclosed a variety of observations that warrant further study,



including risk factors related to timing of exposure to foods, the influence of environmental and dietary factors, and genetics. Ongoing large population-based cohort studies<sup>33,35,71-73</sup> are likely to provide additional insights on prevalence, natural course, and risk factors. These studies fuel approaches for prevention and treatment.

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